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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/975,932 | 10/15/2001 | Daniel G. Chain | CHAIN=1C | 2674 |

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| EXAMINER | |
|---|---|
| CROUCH, DEBORAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | 15 |

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/975,932 | CHAIN, DANIEL G. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *28-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed July 19 and July 24, 2003 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-30 are pending. Claims 28-30 have been withdrawn from consideration. Claims 1-27 are examined below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are to methods for delaying or inhibiting or suppressing the accumulation of an amyloid β peptide or fragment thereof in a brain of a mammal comprising contacting a composition comprising a recombinant DNA molecule containing a gene encoding a recombinant antibody molecule end specific for the N-terminus or the C-terminus of an amyloid β peptide, operably linked to a promoter which is expressed in the central nervous system, a recombinant DNA molecule comprising a gene encoding a recombinant antibody molecule end-specific for the N-terminus or the C-terminus of an amyloid β operably linked to a promoter, and a vector, host cells and a pharmaceutical composition each comprising the DNA.

The method claims are not enabled as the specification fails to provide guidance for the successful delaying, inhibiting or suppressing the accumulation of amyloid β peptide in the brain of a mammal. At the time of filing, the art taught that in general gene therapy for brain related disorders was unpredictable because delivery of the DNA sequences encoding

the therapeutic protein to brain and its subsequent expression could not be adequately achieved. The specification provides no guidance to overcome these art recognized unpredictabilities so that the skilled artisan at the time of filing could have practiced the claimed invention so that a delay, inhibition or suppression of amyloid β accumulation in the brain of a mammal could have been achieved.

The art at the time of filing recognized that intrabody therapies, the administration of DNA sequences encoding antigen binding regions of antibodies, had potential usefulness in the treatment of Alzheimer's Disease (AD). However, the art also taught that intrabody therapy for AD required the development of an efficient means for transferring intrabody coding sequences to neuronal cells in vivo and achieving expression of DNA sequences at an effective level over long periods of time (Jones, page 164, col. 1, lines 1-3 and 22-26). These unpredictabilities in intrabody gene therapy for AD parallel those also acknowledged by the art at the time of filing for intrabody gene therapy in general, which in turn mirrored the unpredictability observed with gene therapy protocols in general. The issues contributing to intrabody gene therapy in general include increasing the proper folding and stability of the intrabodies, especially in the cell's cytosol, and developing algorithms for predicting those epitopes on the target molecules that will be most effective as an intrabody target. This clearly establishes that intrabody gene therapy for AD was not enabled at the time of filing.

The specification does not provide guidance, through discussion or examples, for a delay, inhibition or suppression of amyloid β accumulation in the brain of a mammal by the administration of a composition comprising a DNA molecule encoding a recombinant antibody end-specific for the N or C terminus of an amyloid β peptide. The specification describes a projected method for cloning of huβAPPH/KAβAAV, which is the coding sequence for monoclonal antibody ScFvαAβ contained in an AAV (specification, pages 47-48). Further

experiments are described that would demonstrate that the antibody produced in neuronal cells transformed with huβAPPH/KAβAAV retains it's A/β binding properties. However, no such results are included in the discussion. In addition, the specification does correlate any particular delivery method for huβAPPH/KAβAAV with a delay, inhibition or suppression of amyloid β accumulation in the brain of a mammal. Further, there is no correlation made between delivering any DNA sequence encoding an A/β intrabody using viral vectors, cell targeting moieties or liposomes with a delay, inhibition or suppression of amyloid β accumulation in the brain of a mammal. The specification describes the production of co-transgenic mice containing DNA sequences for an ScFv intrabody sequence and a DNA sequence encoding APP 670/671 mutation. However, there is no outcome described for this mouse. The mouse would not be correlatable to a method of treatment to delay, inhibit or suppress amyloid β accumulation in the brain of a mammal because the mouse had both transgenes at the outset. Transgenesis does not overcome the problems recognized by the art with delivery and expression of intrabody DNA sequences for purposes of AD treatment. Thus, the specification does not supply those teachings absent in the art at the time of filing.

In addition, the specification does not discuss a need that the antibody encoded by the DNA sequence be of the same species as the mammal to which the DNA sequences have been administered. The immune system of the mammal would recognize as foreign an intrabody produced by a delivered DNA sequence that did not match the host, and thus mount an immune response to the intrabody that was not the same species as the host. An immune response would unpredictably affect the antibody's ability to delay, inhibit or suppress amyloid-β accumulation in the brain of a mammal by the antibody.

Thus, for these reasons, at the time of the present invention, the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable

degree of success to delay, inhibit or suppress amyloid β accumulation in the brain of a mammal by administering a DNA sequence encoding a recombinant antibody end-specific for the N or C terminus of an amyloid β peptide. Applicant's specification fails to provide the required guidance for the implementation of the claimed invention.

Applicant's response filed June 19, 2003 states that the enablement rejection made in the previous office action, mailed December 20, 2002, was in error as it was based on Elan/Wyeth Phase II trials. These trials, applicant argued, administered an antibody to Alzheimer's Disease patients and did not reflect the invention as claimed where a DNA sequence encoding a recombinant antibody end-specific for the N or C terminus of an amyloid β peptide is administered to delay, inhibit or suppress amyloid β accumulation in the brain of a mammal. This deleterious effect is demonstrated in the Elan/Wyeth trials discussed in the previous office action. To the extent that the antibody used in the trials was not humanized, the trials are relevant as the claims do not require the antibody being produced via the transfected DNA sequence to be of the same species as the mammal. See previous office action, mailed December 20, 2002, pages 2-4.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-21 and 25-27 state "a pharmaceutical composition." This phrase is regarded as an intended use and such a phrase is not given patentable weight in the art rejections below.

Claims 14-18 and 20-27are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al (1993) Proc. Natl. Acad. Sci. 90, pp. 7889-7893 in view of Seubert et al

(1993) Nature 361, pp. 260-263, Nakamura et al (1995) Neurosci. Lett. 201, pp. 151-154 and Bourbonniere et al (1993) Molec. Brain Res. 19, pp. 246-250 in view of Solomon et al (1995) Proc. Natl. Acad. Sci. 93, 452-455.

Marasco teaches the production of a recombinant DNA molecule encoding a single-chain antibody, which binds to HIV-1 gp120 (abstract). Marasco teaches the sequencing and cloning of $V_H$ and $V_L$ genes of a monoclonal antibody to gp120 to produce a recombinant DNA molecule, which encodes a single-chain antibody that binds to gp120 (page 7889,col. 2, parag. 1). The recombinant gene was inserted into a plasmid vector, the vector subsequently transformed into COS cells and the single chain antibody expressed (page 7890, col. 1, parag. 7 to page 7891, col.1, parag. 3). Marasco does not teach cloning and expressing antibodies directed to the N-terminus or C-terminus of an A/β peptide and its expression in brain cells.

Seubert teaches monoclonal antibody 6C6, which bind to the amyloid-beta N-terminus (page 261, co. 1, parag. 2, lines 5-10).

Nakamura teaches a monoclonal antibody BC05 that recognizes an epitope in residues 35-43 of Aβ (page 152, col. 1, parag1, lines 1-2).

Bourbonniere teaches the APP promoter directs expression of a CAT gene in cultured neuronal cells, NG108-15 (page 246, col. 2, parag. 2, lines 1-8).

Solomon teaches that monoclonal antibodies to βA4, an alternate name for A/β or β-amyloid peptide, prevents the formation of insoluble amyloid fibrils (page 454, col. 1, parag. 1, lines 3-7).

Solomon provides significant motivation for the combination of Marasco, Seubert, Nakamura and Solomon to reach the claimed invention. Solomon teaches that the aggregation of soluble βA4 into insoluble amyloid fibrils is a crucial step in the development of Alzheimer's Disease (page 454, col. 2, parag. 2, lines 1-4). Solomon also teaches that the

prevention or reduction of such aggregation was a main focus of Alzheimer's Disease research at the time of filing (page 454, col. 2, parag. 2, lines 5-8). Solomon even states that investigations were underway at the time of into the ability of monoclonal antibodies and their genetically engineered fragments to suppress aggregation of βA4 in cultured PC-12 neural cells (page 454, col. 2, parag. 3).

Therefore, at the time of filing, it would have been obvious to the ordinary artisan to prepare a recombinant DNA molecule encoding a single chain antibody having Aβ binding activity end-specific for the N-terminus or the C-terminus where the DNA molecule was operatively linked to an APP promoter for expression in neuronal cells, vectors containing the recombinant DNA molecule and host cells transformed with the vector given Marasco teaching methodology for the production of recombinant DNA molecules encoding single chain antibodies and their expression in COS cells as either secreted or non-secreted antibodies, Seubert and Nakamura teaching hybridomas that produce N-terminus and C-terminus end-specific monoclonal antibodies, the monoclonal antibodies being required for the method of Marasco, Bourbonniere teaching the APP promoter as directing expression of a DNA sequence of interest in neuronal cells and Solomon teaching that monoclonal antibodies to A/β (βA4) prevent aggregation of the amyloid peptide. When these teachings are taken with the motivation provided by Solomon that the prevention of Aβ aggregation is a focus of Alzheimer's Disease therapeutic research and that experiments were underway to determine the effect of expressing DNA sequences encoding monoclonal antibodies to Aβ in neuronal cells on Aβ aggregation, the ordinary artisan at the time of filing would have had the requisite teaching, suggestions and motivation to arrive at the claimed invention to determine those DNA sequences encoding monoclonal antibodies against Aβ that had the greatest effect on Aβ aggregation in cultured neuronal cells. As the APP promoter is active in neuronal cells, the cells which express A/β and are damaged by its accumulation, the APP

promoter directing expression of the DNA sequences encoding monoclonal antibodies to Aβ would have been obvious to the ordinary artisan at the time of filing. It would have been obvious at the time of filing to the ordinary artisan to direct expression of the DNA sequence using a promoter known to be active in neuronal cells.

Claims 18 and 19 rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al (1993) Proc. Natl. Acad. Sci. 90, pp. 7889-7893 in view of Seubert et al (1993) Nature 361, pp. 260-263, Nakamura et al (1995) Neurosci. Lett. 201, pp. 151-154 and Bourbonniere et al (1993) Molec. Brain Res. 19, pp. 246-250 in view of Solomon et al (1995) Proc. Natl. Acad. Sci. 93, 452-455 and further in view of Le Gal La Salle et al (1993) Science 259, 988-990, Yang et al (1994) Neurosci. Lett. 182, 287-290 and Cheng (1996) Human Gene Therapy 7, 272-282.

Marasco teaches the production of a recombinant DNA molecule encoding a single-chain antibody, which binds to HIV-1 gp120 (abstract). Marasco teaches the sequencing and cloning of $V_H$ and $V_L$ genes of a monoclonal antibody to gp120 to produce a recombinant DNA molecule, which encodes a single-chain antibody that binds to gp120 (page 7889,col. 2, parag. 1). The recombinant gene was inserted into a plasmid vector, the vector subsequently transformed into COS cells and the single chain antibody expressed (page 7890, col. 1, parag. 7 to page 7891, col.1, parag. 3). Marasco does not teach cloning and expressing antibodies directed to the N-terminus or C-terminus of an A/β peptide and its expression in brain cells.

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Solomon teaches that monoclonal antibodies to βA4, an alternate name for A/β or β-amyloid peptide, prevents the formation of insoluble amyloid fibrils (page 454, col. 1, parag. 1, lines 3-7).

Le Gal La Salle teaches the transfection of sympathetic neurons and astrocytes with an adenoviral vector comprising a gene encoding β-galactosidase operably linked to an RSV promoter, and the production of detectable quantities of the enzyme by the infected cells (page 988, col. 1, parag. 1 to col. 2, line 13).

Yang teaches the transfection of primary hippocampal neurons with a liposome comprising DOTMA and a plasmid comprising a gene encoding β-galactosidase operably linked to a CMV promoter, and the production of detectable quantities of the enzyme by the transfected cells (page 288, parag. 1 and 2, and figure 1).

Cheng teaches the transformation of HeLa cells with a liposome comprising a lipofectin agent, a plasmid comprising a gene encoding β-galactosidase operably linked to a CMV promoter, and transferring complexed to the lipofectin, and the production of detectable quantities of the enzyme produced by the transformed cells. (page 277, col. 1, parag. 3, lines 1-5).

Each of Le Gal La Salle, Yang and Cheng provides motivation for testing various vectors and delivery systems to determine the system that would provide the best expression and/or best inhibition of A/β aggregation in cultured neuronal cells, given the extensive testing performed in each of these references to determine expression conditions.

Solomon provides significant motivation for the combination of Marasco, Seubert, Nakamura and Solomon to reach the claimed invention. Solomon teaches that the aggregation of soluble βA4 into insoluble amyloid fibrils is a crucial step in the development

of Alzheimer's Disease (page 454, col. 2, parag. 2, lines 1-4). Solomon also teaches that the prevention or reduction of such aggregation was a main focus of Alzheimer's Disease research at the time of filing (page 454, col. 2, parag. 2, lines 5-8). Solomon even states that investigations were underway at the time of into the ability of monoclonal antibodies and their genetically engineered fragments to suppress aggregation of βA4 in cultured PC-12 neural cells (page 454, col. 2, parag. 3).

Therefore, at the time of filing, it would have been obvious to the ordinary artisan to prepare a recombinant DNA molecule encoding a single chain antibody having Aβ binding activity end-specific for the N-terminus or the C-terminus where the DNA molecule was operatively linked to an APP promoter for expression in neuronal cells, vectors containing the recombinant DNA molecule and host cells transformed with the vector given Marasco teaching methodology for the production of recombinant DNA molecules encoding single chain antibodies and their expression in COS cells as either secreted or non-secreted antibodies, Seubert and Nakamura teaching hybridomas that produce N-terminus and C-terminus end-specific monoclonal antibodies, the monoclonal antibodies being required for the method of Marasco, Bourbonniere teaching the APP promoter as directing expression of a DNA sequence of interest in neuronal cells and Solomon teaching that monoclonal antibodies to A/β (βA4) prevent aggregation of the amyloid peptide, where the antibody DNA sequences were contained within an adenoviral vector, a liposome or delivered via a cell surface receptor ligand, as taught respectively by Le Gal La Salle, Yang and Cheng. When these teachings are taken with the motivation provided by Solomon that the prevention of Aβ aggregation is a focus of Alzheimer's Disease therapeutic research and that experiments were underway to determine the effect of expressing DNA sequences encoding monoclonal antibodies to Aβ in neuronal cells on Aβ aggregation, the ordinary artisan at the time of filing would have had the requisite teaching, suggestions and motivation to arrive at

the claimed invention to determine those DNA sequences encoding monoclonal antibodies against Aβ that had the greatest effect on Aβ aggregation in cultured neuronal cells. As the APP promoter is active in neuronal cells, the cells which express A/β and are damaged by its accumulation, the APP promoter directing expression of the DNA sequences encoding monoclonal antibodies to Aβ would have been obvious to the ordinary artisan at the time of filing. It would have been obvious at the time of filing to the ordinary artisan to direct expression of the DNA sequence using a promoter known to be active in neuronal cells. Also, it would have been obvious to determine effective DNA transfer and expression using the delivery systems claimed given the knowledge in the art at the time of filing that they effectively expressed a gene of interest in transfected or transformed cultured neurons or HeLa cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

May 21, 2004